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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/448,727	05/24/95	BURNETT	D-242 CIP-C

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U S PATENT OPERATIONS RJM
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EXAMINER	
SIDBERRY,H	

ART UNIT	PAPER NUMBER
1802	6

DATE MAILED: 01/30/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 9-12, 14-22, 24-26, 28, 30, 35 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 9-12, 14-22, 24-26, 28, 30, 35 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40517

This Application is a DIVISION of application Serial No. 08/034,460 filed 3/18,1993.

The Examiner acknowledges the Amendment filed 5/24/95 cancelling claims 1-8.

The Examiner acknowledges the Amendment filed 9/9/96 updating the continuing data in the specification and further compliance with Sequence Rules 37 CFR 1.821-1.825.

Claims 13, 23, 27, 29, 31-34 are now cancelled.

Claims 9, 12, 14, 17-19, 22, 24, 28, 30 are amended.

Claims 9-12, 14-22, 24-26, 28, 30, 35 are pending

Applicant has submitted remarks with the PRELIMINARY AMENDMENT filed 9/9/96.

Applicants remarks have been considered.

The Examiner acknowledges the summary of the prosecution history in the parent application.

Applicant's claims in the prior application were directed to the DNA. The claims before the Examiner are not to DNA, but analogs of pertussis toxin which are non-toxic and an "improved vaccine" comprised of said analogs.

The prior art cited against the DNA claims is not relevant to these claims.

Applicant also contends that the scope of the claims is reasonable and fully supported, citing the experimental results in Tables 1 and 2. The Examiner, has given consideration to Applicant's remarks, however the remarks do not serve to negate the 35 USC 112 1st paragraph issues which will be set forth below.

Although Applicant urges that the scope is limited and that the breadth of the claims is reasonable, however, it is viewed that the specification only enables analog Arg9 to Lys.

Applicant also urges that the <u>in vivo</u> results performed on mice using the Arg9 Lys analog, and similar results are evidenced

by the articles and Patent listed in the remarks enables the claimed analogs.

However, these analogs are not the same as that disclosed by Applicant. However, it is noted that the prior discloses a number of pertussis analogs, some of which effected protection, while others did not. The disclosure of other analogs which did not function to protect and were not free of enzymatic activity, only serve to support that the scope of the claim, is not commensurate with the disclosure.

Regarding the prior art issues, Applicant cites Locht and Keith, Science contending that the reference does not render obvious the claims by suggesting the modification of the region between Val7 and Pro14, because there is no "teaching of specific amino acid residues". The prior art of Keith et al US Patent 4 883 761 will be applied against the claims.

It is noted that Applicants claims do not recite or require any "specific amino acid residue", but recite substitution of "one or more amino acid residues in the region of valine 7 through proline 14".

The prior art teachings suggest the modification of this particular region, and as such render the claims which do not recite a particular amino acid residue obvious.

The disclosure is objected to because of the following informalities: The drawings are objected to under 37 CFR 1.84 for the reasons set forth on the PTO form 948.

The oath/declaration is objected to because it is inconsistent with the continuing data submitted 9/9/96, as it fails to reference the 07/232,482 application filed 9/17/88. Appropriate correction is required.

Claims 9-12, 14-22, 24-26, 28, 30, 35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing

to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is indefinite because there is no antecedent basis for "the" Bordetella exotoxin; "the" naturally occurring; "the" substitution; "the" region bounded; in the claim.

Claims 10 and 19 are vague and indefinite in the recitation of "further comprises at least one major epitope know to important in providing immunoprotection." It is unclear what Applicant intends be encompassed by this term.

Claim 14 is indefinite because there is no antecedent basis for "the" arginine 9 site in the claim.

Claim 17 is indefinite because there is no antecedent basis for "the" amino-terminus in the claim. It is suggested that applicant amend the claim to recite "which includes an amino-terminus methinylvalyl sequence". This would serve to define the location of this sequence.

Claim 18 is indefinite because there is no antecedent basis for "the" amino acid sequence in the claim.

Claim 19 is indefinite because there is no antecedent basis for "the" naturally occurring; "the" substitution; "the" region bounded by valine in the claim.

Claim 24 is indefinite because there is no antecedent basis for "the" arginine 9 site in the claim.

Claim 35 is indefinite because there is no antecedent basis for "the" amino acid sequence in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use

the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification as originally filed does not now provide support for the invention as now claimed.

Applicant has amended the claims to recite that the analog is "free" of enzymatic activities associated with exotoxin reactogenicity." The specification does not provide support for the use of the term "free", as the specification indicates that the analogs are "substantially free".

In fact, Burnette et al (Science 242:72-74,1988) indicate that an analog altered at Arg9 lys "had reduced enzymatic activity".

Thus, the analog(s) are not free of enzymatic activity.

Claims 12, 22 has been amended to delete the term "substantially". However, the deletion of this term from the claim(s) suggests that subunit S1 has no enzymatic activity. The specification indicates that the analogs are "substantially free of enzymatic activity." The deletion of the term "substantially" is therefore new matter.

The claims recite elements without support in the original disclosure. In re Rasmussen, 650 F2d 1212 (CCPA, 1981) New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See MPEP 608.04 to 608.04(c)

Claims 9-12, 14-22, 24-26, 28, 30, 35 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 9-12, 14-26, 28, 30, 35 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the pertussis analog Arg9 to Lys.

Applicant claims analogs of S1 subunit of pertussis toxin, where the analogs differ in amino acid sequence from the native S1, by the substitution of one or more amino acid residues in the region bounded by valine 7 to proline 14. The resulting analogs are required to retain biological activity, to induce neutralizing antibody and be free of enzymatic activities associated with exotoxin reactogenicity.

It in noted that the Table I shows other analogs of the S1 subunit. However, the specification sets forth no data which establishes that these "analogs" fulfill the criteria set forth in the claims. The analogs have not been shown to inactive, either in vitro or in vivo,, nor have they been established as an "improvement" over the prior art.

The claims further recite "one or more" residues, however, the specification does not teach which other residues may be altered in the region, to obtain a pertussis toxin analog which can elicit toxin neutralizing antibody and is free of enzymatic activities associated with exotoxin reactogenicity.

Black et al (Ann Sclavo No 1-2, pp 175-182, 1986) in a discussion of non-toxigenic mutants of Bordetella pertussis, set forth some of the issues regarding nontoxic mutants.

Will a mutant which is reduced in its toxicity still engender a protective immune response in humans? This is an important issue for two reasons:

Conceivably, an enzymatically inactive pertussis toxoid might be insufficiently immuno-stimulatory for a protective immune response.

It is unclear whether animal models, which have traditionally, been used to assess pertussis vaccine efficacy, can accurately predict the success in humans of a genetically created toxoid. (see page 180)

Pizza et al, cited, indicate that they generated more than 30 strains of Bordetella in which most of the mutations known to reduce enzymatic activity were introduced, alone or in combination. However, most of the mutants were not useful, because they were produced in low yield, not assembled, or found to be toxic. (see page 499)

Burnette et al (Science 242:72-74, 1988) indicate, after assaying the reactivity of double-residue substitutions, as well as the mutant in which the homology box had been deleted, reactivity [with the protective mAB 1B7 was significantly diminished or abolished. If this protective S1 epitope is to be retained in a subsequent vaccine preparation, only those analogs with single substitutions in the homology box would be potentially useful. (see page 73 3rd col.)

Burnette et al further indicate that the analog which had methionylvaline [had] enzymatic activity. (see page 73, 1st column) Moreover, Burnette et al teach that the analog tyr8 Phe had enzymatic activity equivalent to the unaltered pertussis toxin, similarly Asp11 Glu; Ser12 Gly and Arg13 Lys. (see Table page 73)

Thus, Burnette et al indicate that only the Arg9 Lys mutation yielded a "useful" S1 analog.

The teachings of Pizza et al and Burnette et al suggest that it is unpredictable, selecting amino acids which can be substituted even in the region limited to valine 7 to proline 14 of the S1 subunit.

At the time the invention was filed, the pertussis art considered it unpredicatable determining those amino acid residues which could be substitutued in pertussis toxin without affecting either its antigenicity and/or toxicity. Furhter, the art questioned whether the standard animal model whcih was considered predictive of success in jhumans, could be reasonably

applied to these mutated toxins. Although the region bounded by Val7 to Pro14 encompasses only eight amino acid residues, the later teachings of Pizza et al and Burnette et al support the trial and error of selecting amino acid residues which may be substituted in that region and still result in a "useful" pertussis toxin analog.

Although the specification sets forth more than one example, as Applicant may urge that this is sufficient guidance, it is noted and Burnette et al later evidences that "only one" analog proved to be useful.

Thus, the specification fails to enable the claim limitation of substitution of "more", regarding the substitution of amino acid residues, as the specification fails to teach other residues which may be altered, resulting in pertussis analogs having the required properties as of the claims.

Applicant claims analogs of pertussis toxin S1 subunit and an "improved" vaccine comprised of the S1 subunit analogs.

The specification sets forth data showing mice immunized with "crude recombinant" S1, and recombinant S4.

The specification does not show protection, with the S1, but only an "increase in survival time". Immunization with "an adjuvant" and S1 protected "a number of mice" and rS1 resulted in protection against challenge. (see page 19 of the specification).

The data in the specification does not effectively enable the claim to an "improved" vaccine, as the disclosed vaccine, was not, in fact, an improvement of the prior art vaccines.

The specification indicates that "later studies have not confirmed immunoprotection against intracerebral challenge with B. pertussis mouse virulent stain 18323."

Therefore, the specification fails to enable the claim to an improved vaccine, as the disclosure does not teach how to achieve such using the claimed analogs.

Claim 28 recites that the subunits S2, S3, S4, S5 have been genetically engineered. The use of the term "genetically engineered", suggests that subunits S2-5 have been subjected to some type of modification.

However, the specification does not teach the modification of any of the bordetella subunits beyond the inclusion of a methionylvalyl sequence.

Applicant also claims the exotoxin selected from the group consisting of B. pertussis, B. parapertussis and B. bronchiseptica.

However, Pizza et al (Science 246:497-500, 1989) indicates that the species parapertussis and bronchiseptica do not normally produce pertussis toxin. (see page 498, 3rd paragraph) They have a defective promoter region and but do not produce the toxin.

The specification does not teach that the PTX operon in the recited species must be "replaced with an operon containing a functional promoter" and thus does not provide an enabling disclosure regarding the claim to the exotoxin from other Bordetella species. See M.P.E.P. 706.03(n) and 706.03(z).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this

section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 9-12, 14-26, 28, 30, 35 are rejected under 35 U.S.C. § 103 as being unpatentable over Keith et al US Patent 4 883 761.

Keith et al US Patent 4 883 761 teach the cloning and expression of pertussis toxin subunits S1, S2, S3, S4 and S5 for the vaccinogenic purposes.

Keith et al teach the region encompassed by valine7 and proline14 of pertussis toxin is homologous to the same region in cholera toxin (CT) and heat labile enterotoxin (ET) which is the functional domain for a catalytic activity in the subunits for all the toxin. (see Abstract and col. 16, Table 4, col. 17, lines 40-50; col. 21, lines 45-68)

Keith et al suggest modification of this region.

Keith et al teach that the cloning of the pertussis toxin genes provides a means for genetic manipulation of and for producing antigenic peptides (toxins) for the synthesis of new generation of vaccines against pertussis.

Moreover, Keith et al teach that the such manipulation of the pertussis toxin gene allows the creation of new, manipulated toxins retaining antigenicity against pertussis, but being devoid of undesirable side effects. (see col. 2 lines 60-68)

Keith et al teach that "cloned and sequence pertussis toxin genes are useful for the development of an efficient and sager vaccine against whooping cough. By comparison to other toxin genes with similar biochemical functions and by physical identification of the active sites either for ADP-ribosylation of the S1 subunit or the it is now possible to modify those sites by site-directed mutagenesis of the B. pertussis genome. These modifications could abolish the pathobiological activities of

pertussis toxin without hampering its immungenicity and protectivity (see column 23 and 24)

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify this region "bounded by valine7 to proline14" in the enzymatically active S1 subunit for the synthesis of new generation of pertussis toxins, with a reasonable expectation of obtaining modified pertussis toxin which retain antigenicity against pertussis, but are devoid of undesirable side effects.

The Art Unit location of your application in the Patent and Trademark Office has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1802.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to H. Sidberry whose telephone number is (703) 308-0170.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to the Group 1800 by facsimile transmission. The CM1 1802 fax Center number is (703- 308-4242)

Sidberry/hfs
January 15, 1997

Primary Examiner
GROUP 1800